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## Superior sulcus tumors

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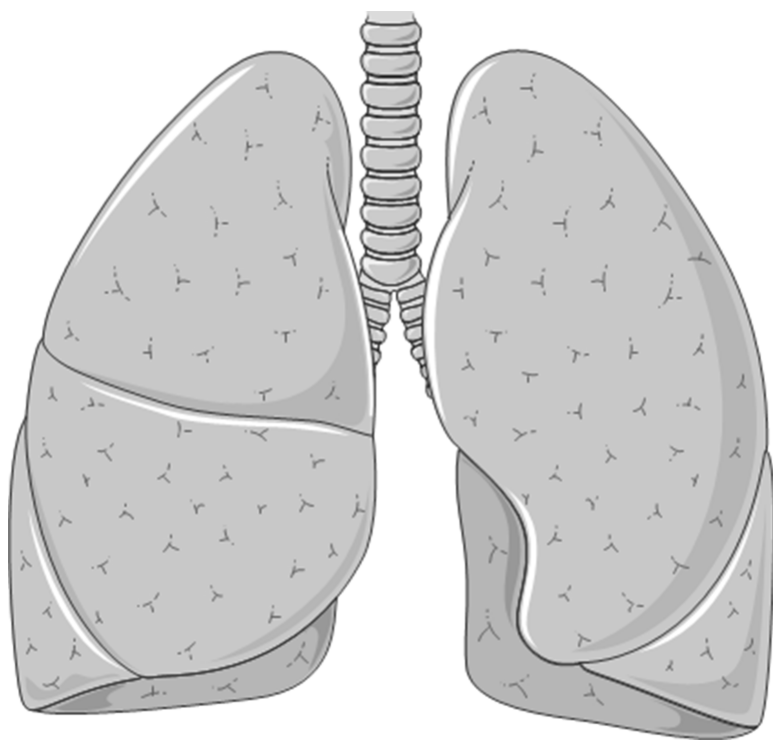
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# PART I

## INTRODUCTION



# CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

## GENERAL INTRODUCTION

Non small-cell lung cancer (NSCLC) accounts for about 80% of all lung cancers and is the number one cause of cancer-related mortality in the Netherlands.<sup>1</sup> Superior sulcus tumors, or Pancoast tumors, are a subtype of NSCLC. They are distinguished by their location at the pulmonary apex and invasion of surrounding structures. Superior sulcus tumors account for less than 5% of all NSCLC.<sup>2,3</sup>

When first described by Henry Pancoast in 1932, superior sulcus tumors were considered incurable.<sup>4,5</sup> Pancoast described a tumor at the pulmonary apex associated with pain, Horner's syndrome, bone destruction and atrophy of the hand musculature.<sup>4</sup> These signs and symptoms are caused by invasion of the structures surrounding the pulmonary apex, such as the brachial plexus, stellate ganglion and the chest wall.

Over the years, evolution in the management of these patients with potentially resectable tumors has led to improved survival rates.<sup>5</sup> In the 1950s treatment with induction radiotherapy followed by resection made cure a possibility for some patients, and for 40 years this remained the standard treatment.<sup>6,7</sup> There were some subsequent improvements in surgical techniques for T4 tumors with invasion of the subclavian vessels and the spine<sup>8-10</sup>, but no major changes in outcome were achieved until the early 1990s. Prior to this period, complete resection rates did not exceed 60-70%, recurrence rates were high (>40%) and 5-year survival rates remained stable at approximately 30%.<sup>5</sup> In the early 1990s, chemotherapy was added to the pre-operative treatment regime. Initially, radiotherapy was administered sequentially, after chemotherapy. Subsequently, concurrent induction chemoradiotherapy was preferred. This strategy is associated with complete resection rates of more than 90% of T3, and 85% of T4 patients, and treatment failure, which had previously been due mainly to local recurrence, was now predominantly a result of distant metastasis, mainly to the brain.<sup>3,5</sup> Nowadays, in many institutes, standard therapy for superior sulcus tumors is concurrent chemoradiation followed by resection, resulting in 5-year survival rates of over 50%.<sup>3,5,11-17</sup>

Further improvement in the clinical outcome for patients with superior sulcus tumors is necessary. One observation is that about 1/3 of patients achieve a pathological complete response to induction chemoradiotherapy. Several studies have identified a complete pathological response or the presence of 10% or fewer vital tumor cells in the resected

specimen as major predictors of long term survival.<sup>2,5,12-14,18-20</sup> Development of diagnostic modalities that could predict pathological response preoperatively might be useful. First, if available, they could make response-directed treatment strategies possible. For example, induction chemoradiotherapy could be intensified when there was no or minimal response. Secondly, because it is unknown whether resection of a tumor that has responded completely to induction therapy is necessary, being able to predict this without an operation would allow the strategy of 'no-surgery' in these patients, to be tested.

With improvement in survival for patients with operable superior sulcus tumors, the number of long-term survivors is increasing. This further emphasizes the importance of patient reported outcome measures. These include amongst others, quality of life and functional impairment after treatment. This is a second area in which outcomes might be further improved. Damage to lung tissue, chest-wall, brachial plexus, and large vessels by en-bloc resection, radiotherapy and chemotherapy can have a significant impact on quality of life and some patients experience decreased lung and arm function and chronic post-operative pain.<sup>5</sup> The risk to arm function is especially important in superior sulcus tumors, compared to other types of NSCLC, because the tumor is located in the cervico-thoracic junction, where there are many structures that are important for arm function. There is currently a lack of data concerning the quality of life of superior sulcus tumor patients. In addition, there is only limited data concerning arm function, most of which is not systematically reported.<sup>5,9,21-23</sup> More knowledge is needed about these important treatment-related outcomes in order to provide holistic patient care and maximize the benefits of treatment.

Of all patients with superior sulcus tumors, about 30% are amenable to surgery.<sup>24</sup> The VU University Medical Center (VUmc) is a tertiary referral center for superior sulcus tumors and each year, approximately 10-15 patients are operated on. Decision-making and treatment is performed by a multidisciplinary team consisting of surgeons, pulmonary physicians, radiation oncologists, pathologists, radiologists and nuclear physicians, which is required for the optimal management of these tumors. This has stimulated and facilitated the research that is contained in this thesis, which focuses on the management of patients with operable superior sulcus tumors. This multidisciplinary approach to the management of superior sulcus tumors is essential to be able to offer optimum care and to extend the boundaries of what is possible for individual patients.

## AIMS OF THIS THESIS

The specific aims of the work in this thesis are summarized as follows:

- To evaluate the results of trimodality treatment at VUmc and identify prognostic factors for improved survival.
- To study whether anatomical and metabolic parameters can predict the response to induction chemoradiotherapy.
- To evaluate patient reported outcomes and gain insight into the effects of trimodality therapy on arm function and quality of life.
- To highlight the role of multidisciplinary surgical expertise in delivering complex operative therapy to individual patients and to illustrate the challenges of major resections.

## OUTLINE OF THE THESIS

### PART I: Introduction

A general introduction and outline of the thesis is given in **Chapter 1**. **Chapter 2** gives a comprehensive overview of current insights into the diagnosis and management of superior sulcus tumors. In **Chapter 3**, the results of trimodality treatment for superior sulcus tumors according to a standardized institutional protocol are described and compared to the results reported in the literature. Additionally, prognostic factors for survival are investigated and evolution of the protocol over time is discussed.

### PART II: Response evaluation in superior sulcus tumors

Pathological response to trimodality treatment is identified as an important prognostic marker for survival. In **Chapter 4**, the value of changes in tumor volume measured on CT for the prediction of pathological complete response is analyzed. In addition, a semi-automatic method for serial volume assessment based on deformable image registration is evaluated. Although tumor size is of prognostic importance, expressed by its incorporation in the TNM-classification, large tumors can still be sterilized with chemoradiotherapy. In **Chapter 5**, we investigated whether pre-treatment tumor size can be used to predict pathological

response following trimodality treatment. Second, we analyzed whether moderate dosages of radiotherapy (45-50 Gy) are enough to sterilize tumors, regardless of tumor size. Since tumor size and volume only give anatomical information and therefore might not be sensitive enough to predict tumor response to induction treatment, in **Chapter 6**, metabolic activity measured by FDG-PET/CT-scanning and its capability to predict pathologic response is investigated.

### **PART III: Arm function and quality of life**

**Chapter 7**, describes the arm function and quality of life in a cohort of patients that underwent trimodality treatment for a superior sulcus tumor. The hypothesis that treatment on the dominant side and resection of the T1 nerve root leads to worse functional outcomes is tested. In addition, to gain more insight into the influence of trimodality treatment on functional outcome, arm function and quality of life were subsequently investigated in a prospective cohort of superior sulcus tumor patients and outcomes were measured the day before and 3 and 12 months after resection of the tumor. Results of this study are reported in **Chapter 8**.

### **PART IV: Complex surgery and the challenge of extensive resections**

In this part 2 informative cases are described, highlighting complex multidisciplinary surgical possibilities and the challenges associated with extensive resections. In **Chapter 9**, a patient treated for a superior sulcus tumor invading the thoracic spine is described to illustrate the possibilities for curative treatment with extensive resections in individual patients. A second patient is described in **Chapter 10**. The case demonstrates the challenges and possible complications of resections of superior sulcus tumors that invade the spine.

Finally, the results of all studies in this thesis are summarized, discussed and put into perspective in **Chapter 11**. A Dutch translation of this chapter is provided in **Chapter 12**.



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